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APPLICATION NUMBER 087776-350	FILING DATE 04/18/97	FIRST NAMED APPLICANT MACLEAN	ATTY. DOCKET NO. A 117-231
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HM12/0202

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EXAMINER

UNGAR, S
ART UNIT PAPER NUMBER

1642

DATE MAILED 02/02/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 12/17/98
- ☒ This action is FINAL.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 20, 22-30, 32-42 is/are pending in the application.
Of the above, claim(s) 23 & 35 is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 20, 22, 24-30, 32-34 & 36-42 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

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1. The request filed on December 12, 1998 (Paper No. 15) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/776,350 acceptable and a CPA has been established. An action on the CPA follows.

2. The Claims 20, 22, 24-30, 32-34 and 36-42 are currently under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Because all claims are drawn to the same invention claimed in parent application Serial No. 08/776,350 and no additional arguments or amendments to the claims have been submitted, claims 20, 22, 24-30, 32-34 and 36-42 remain rejected for the reasons previously disclosed in Paper No. 10, filed March 8, 1998 as follows:

5. The following objections are being maintained:

The amendment to the specification replacing "in published.....00179)"by -- USSNs...-- has been entered. The attempt to **incorporate essential materials** into this application by reference to published patent application WO92/13943 disclosed on page 4 of the specification, or by amendment to replace the world patent with numbers of patent application which have not been allowed is improper because essential materials can only be incorporated by reference to (1) a U.S. patent or (2) an allowed U.S. application meeting the conditions set forth in MPEP 608.01(p) section B. See *In re Fouche* 169 USPQ 429:439 F.2d 1237 (CCPA 1971).

6. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

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7. Claims 20, 22, 24-30, 32-34 and 36-42 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Section 11 of Paper No. 6 on pages 6-7.

Applicant argues that (a) although only HSV-1 strain 1716 is exemplified, the invention does not relate to how to obtain strains of HSV-1 which are attenuated by virtue of inactivation of the gamma 34.5 gene of each RL, (b) techniques for achieving inactivation had been taught in US Patent No. 5,328,688 and WO 92/13943, therefore the specification does not need to teach explicitly how to inactivate the gene or to accurately predict the phenotype of mutated HSV-1. The arguments have been noted but have not been found persuasive because (a) the mutant HSV-1 virus is clearly a critical element of the invention since, clearly, without access to a mutant HSV-1 that functions as claimed it would not be possible to practice the claimed invention (b) although techniques for the critical element of inactivation have been taught in US Patent No. 5,328,688 and WO 92/13943, neither of the cited prior art have been incorporated into the specification by reference. Applicant's arguments have not been found persuasive and the rejection is maintained.

8. Claims 25-29 and 36-39 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Section 12 of Paper No. 6 on pages 7-9.

Applicant argues that a skilled person would know where to make deletions and indeed, how to modify the gamma 34.5 gene of each HSV-1 RL with the expectation of providing a virus with the phenotype of interest because (a) it was known in the art how to obtain strains HSV-1 that were attenuated by virtue of

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inactivation of the gamma 34.5 gene of each RL, (b) modifications of Bam H1 ϵ fragment is described in WO 92/13943 and US 5,328,688. The arguments have been noted but have not been found persuasive because (a) the claims as written encompass a broad variety of genetic manipulations that go well beyond the general knowledge in the art. The specification does not teach how to modify, that is by deletion, insertion, substitution or rearrangement, the BamH1 ϵ restriction fragment of the RL terminal repeat so that the invention will function as claimed. Without specific disclosure as to the size, exact location and nature of the modifications, one of skill in the art would not know where to make the modification with the expectation of producing a virus with the phenotype of interest (b) it appears that modified BamH1 ϵ fragments are a critical element of the invention as claimed, however, the specification does not teach how to modify the fragments commensurate in scope with the claims and the cited art has not been incorporated into the specification by reference. Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

9. Claims 20, 22, 24-30, 32-34 and 36-42 are rejected under 35 U.S.C. § 103 as being unpatentable over Market et al (Neurosurgery, 32597-603, IDS item) in view of WO 92/13943 (IDS item) essentially for the reasons disclosed in Section 15 of Paper No. 6 and further in view of Applicant's response of December 24, 1997 (Paper No. 8).

The claims are drawn to a method of treating a tumor in the central nervous system of a human, comprising (1) administering to said human an effective amount

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of a mutant HSV-1 wherein the mutant virus is a mutant strain 17 virus which has a non-functional gamma 34.5 gene in the long repeat region, (2) wherein the cancer is a brain tumor, (3) wherein the cancer is a metastatic tumor, (4) wherein the mutant strain 17 virus has been modified within the Bam HI Δ fragment of the long repeat region by deletions ranging from 0.1 to 3 kb, (5) wherein the virus strain is 1716, (6) wherein the mutant virus is administered directly into the cancer.

Applicant's arguments drawn to the rejection of claims 20, 22, 24-30, 32-34 and 36-42 in Paper No. 8 are relevant to the instant rejection.

Applicant argues that new claims 20 and 30 have been limited to features of canceled claims 21 and 31 to deal with this rejection. The argument has been noted but has not been found persuasive because the amendment of the claims to limit the treatment to "human" rather than mammal does not overcome the rejection under 35 USC 103. Applicant states, on pages 6-7 of Paper No. 8 that (a) it was known by the skilled person that viral therapy was proposed for the destruction of tumors, including brain tumors (Applicant points to references 2-7 listed on pages 49-50 of the specification as evidence), (b) pioneering experiments with HSV showed a dose-dependent improvement in survival of nude mice bearing intracranial human gliomas following intratumoral therapy with mutant HSV-1, © HSV-1 mutant R3616 improves the outcome of nude mice bearing intracranial gliomas (and here cites the paper cited in the 103 rejection of Paper No. 6, Market et al), (d) there is a clear scientific rational for the present invention and (e) suggests that the invention would be expected to work in humans and in other animal models.

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As clearly stated by Applicant, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the mutant HSV-1 of WO 92/13943 into the method of Market et al for the treatment of cancer in a human for the reasons disclosed in Paper No. 6 and further because Applicant has demonstrated that given the state of the art, there is a clear scientific rationale for the present invention and it would be expected to work in humans. One of ordinary skill in the art would have been motivated to substitute the mutant HSV-1 of WO 92/13943 into the method of Market et al for the treatment of cancer in a human for the obvious benefit of specificity of treatment of cancer in dividing cells.

10. All other objections and rejections recited in Paper No. 6 are withdrawn.

11. No claims allowed.

12. This is a CPA of applicant's earlier application S.N. 08/08/776,350. All claims are drawn to the same invention claimed in the earlier application and, although applicant has filed request for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d), no Amendment or Response containing either arguments drawn to the instant rejections or amendments to the claims has been submitted. Thus, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). See M.P.E.P. § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF

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THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

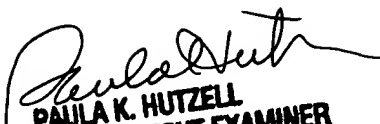
Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

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Susan Ungar
January 11, 1999


PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER